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An outbreak of Japanese encephalitis in a non-endemic region of north-east India

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Abstract

Background There are few comprehensive reports of epidemic Japanese encephalitis in a previously unaffected region. We report our experience of a first-ever outbreak of it in Sonitpur District, Assam, India, with 45 laboratory-confirmed cases at a single hospital.

Method Between 2 July and 11 August 2008, patients meeting the WHO definition of acute encephalitis syndrome were assessed in a single hospital and had tests including blood and cerebrospinal fluid for Japanese encephalitis antibody titres.

Results Ninety-six cases meeting the definition of acute encephalitis syndrome were identified with 45 cases of Japanese encephalitis confirmed by cerebrospinal fluid or blood results. For Japanese encephalitis positive patients, mean age was 36 (range 4–80). Of the 45, 11 (24%) died and a further 21 (47%) had significant residual deficits. Focal neurological signs (40%) and seizures (25%) were common.

Conclusion An effective Japanese encephalitis vaccine is the key intervention for limiting the population impact of this disease. Identification of these cases led to a district-wide mass vaccination campaign.

Keywords: acute encephalitis syndrome, Japanese encephalitis, vaccination programme

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Introduction

Japanese encephalitis (JE), a serious neurological condition caused by the Japanese encephalitis virus (JEV), is a significant cause of mortality and morbidity in the Indian subcontinent, China, south-east Asia and the western Pacific.[1] By best estimates, worldwide there are 65,000 cases of JE annually.[2] Subclinical JEV infection is even more common with more than 100 subclinical infections for every clinical case of encephalitis.[3] JE is a serious condition with 20–25% mortality and a further 50% with significant neurological disability.[1] Because of the high rate of subclinical infection, adults living in endemic regions quickly develop immunity and cases of JE occur predominantly in children.[1] There is no proven effective treatment that mitigates either mortality or morbidity from JE. Vaccination is effective and prevention of JEV infection is the mainstay of reducing the number of deaths and disability caused by the disease,[4] with vaccination programmes targeting children in these areas an obvious way of preventing serious disease.

In non-endemic areas, the case for a JE vaccination programme is less strong. What then happens when JE spreads to a non-endemic area? In order to establish a new vaccination programme, four elements are required: i) clinical identification of new cases of fever with encephalitis as likely to be due to JEV, ii) collection of adequate blood and cerebrospinal fluid (CSF) samples in new cases for testing, iii) access to high quality JE testing facilities to establish the diagnosis and iv) planning and delivery of a vaccination programme to at risk individuals (particularly children) as soon as is practical.

In India, healthcare resources are limited, per capita incomes are low and a very high proportion of health costs have to be met by the patient.[5] In non-endemic areas, it is unlikely that new cases of fever and neurological symptoms are tested for JE, especially in areas where malaria is common, with the assumption that these cases are smear- and rapid-test-negative malaria. This failure of identification contributes directly to low reporting of JE cases and delays in establishment of an effective vaccination programme.

We report details of an outbreak of JE in Sonitpur District, Assam, north-east India, an area where JE had not been previously reported. This provided an opportunity to study the presenting features, disease course, laboratory and imaging findings, and outcome in a population naïve to JE infection as

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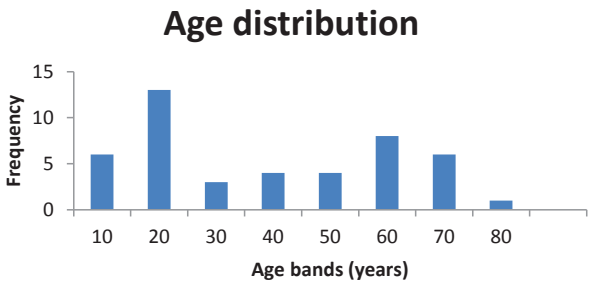
Table 1 Age distribution of Japanese encephalitis positive cases

Age bands (years)	Frequency n = 45
0–10	6 (13%)
11–20	13 (29%)
21–30	3 (7%)
31–40	4 (9%)
41–50	4 (9%)
51–60	8 (18%)
61–70	6 (13%)
> 70	1 (2%)

Figure 1 Age distribution of Japanese encephalitis positive cases



well as providing evidence to launch a vaccination programme in the region. The findings of this study also have relevance to the identification of occasional cases of JE in non-endemic areas in the developed and developing world and in sick travellers returning from endemic areas.

Methods

This was a prospective observational study that took place at Baptist Christian Hospital, Tezpur, Assam, India; a private 100-bed hospital in a town of approximately 100,000 but serving a large, predominantly poor, rural catchment. The hospital medical unit was staffed by two physicians and had a 10-bed high dependency unit with two ventilators. CT scanning and basic laboratory were available on site. The costs of the hospital stay, tests and treatment were borne by patients and their families apart from the tests for JE which were provided free of charge.

The participants were all patients admitted between 2 July 2008 and 11 August 2008 with an acute encephalitis syndrome (AES) defined as any person presenting with a febrile illness, testing negative for malarial parasites on thin blood film and fast immunochemical tests, with altered mental status (reduced level of consciousness, personality or behavioural change), with or without other neurological signs and/or seizures of new onset, i.e. less than 7 days (WHO case definition).

Demographics and presenting features of the illness were recorded on a standard 'acute encephalitis syndrome' paper form, developed after the first few days of the outbreak and subsequently entered into an electronic database. Results of blood tests, CSF, and imaging were recorded. Outcome at hospital discharge was recorded as either 'dead', 'poor' or 'fully recovered'. To meet criteria for 'fully recovered' the patient had to have no neurologic deficit and be able to say the numbers 1 through 10, forwards and backwards in their own language.

Japanese encephalitis testing

At the time of this outbreak, no facilities were available for JE testing at Baptist Christian Hospital. Serological testing for JE was performed at the Regional Medical Research Centre, Indian Council for Medical Research, north-east region, Dibrugarh. Acute blood and CSF, along with convalescent sera (when available), were collected from all patients presenting with AES. The first set of samples from 20 patients were packed in ice and carried by hand on an overnight public bus to Dibrugarh from Tezpur. Two further sets of samples were transported to Dibrugarh during the outbreak. The samples were screened for the presence of anti JEV specific IgM antibodies using IgM capture ELISA (National Institute of Virology, Pune, India). A positive result was based on the criterion described in the kit manual. Briefly, a sample was considered positive when its optical density exceeded the optical density of the negative control by a factor of 5.

For the purposes of this report, 'JE positive' required a compatible history and examination, and positive testing for JEV infection in serum, CSF or both.

Simple descriptive analysis was used. Unpaired T-tests were used to compare different outcome groups. This was an observational study that did not fall within the remit for formal ethics committee review.

Results

From 2 July 2008 to 11 August 2008, 96 patients meeting our criteria for AES were admitted. No samples of either blood or CSF were received by the reference laboratory for 5 patients. Of the remaining 91 patients, 45 (49%) had positive tests for JE.

For the 45 positive patients (hereafter JE+), mean age was 35.4 (SD 22.5, median 34.0, range 4–80). Although 19/45 (42%) were under the age of 20, above this age there were cases in all age groups with 15/45 (33%) older than 50 (Table 1 and Figure 1).

At presentation (Table 2), all patients had a history of fever, with mean (SD) duration of 4.5 (1.7) days. Forty-two (93%) patients at presentation had altered mental status and mean (SD) Glasgow Coma Score (GCS) of 10 (3.4). Of the 3 patients without altered mental status at presentation, all had a combination of fever, headache and abnormal CSF, with one of these becoming confused and the other two having a benign course with full recovery. Focal signs (36%) and seizures (24%) were frequent with the latter often difficult to control. Extrapyramidal features were not specifically recorded but rigidity was only prominent in patients in coma. No patients presented with flaccid paralysis.[1]

Table 2 Clinical and laboratory features

	All n = 45		Poor outcome n = 32		Fully recovered n = 13	
Variable	**Mean/n**	**SD/%**	**Mean/n**	**SD/%**	**Mean/n**	**SD/%**
Age, mean	35.4	22.5	38.0	24.3	28.8	16.1
Male, n	22	48.9	16	50	6	46.2
Presenting features						
Fever, n	45	100	32	100	13	100
Fever duration, days	4.5	1.7	4.5	1.7	4.5	1.9
Headache, n	20	44.4	12	37.5	8	61.5
Altered mental state, n	42	93.3	31	96.9	11	84.6
Altered mental state duration, days	1.5	1.1	1.5	0.8	1.7	1.5
Seizure, n	11	24.4	9	28.1	2	15.4
GCS, units (range 3–15)	10.0	3.4	9.4	3.1	11.5	3.5
Temperature, ^{0}C	37.9	1.1	38.0	1.1	37.7	1.0
Neck stiffness, n	22	48.9	15	46.9	7	53.8
Focal neurological signs, n	16	35.6	14	43.8	2	15.4
Signs of raised intracranial pressure, n	9	20.0	6	18.8	3	23.1
Laboratory results, blood						
Hb, g/l	112.7	18.7	111.7	17.5	115.0	21.8
White blood count/microl	13.7	6.5	14.0	7.0	12.9	5.1
Neutrophils, %	81.4	6.9	82.4	7.1	79.2	6.1
ESR, mm/h	45.9	27.6	44.8	24.6	48.4	35.0
Creatinine, mmol/l	95.4	87.5	102.2	104.3	79.8	11.8
Bilirubin, mmol/l	17.1	23.6	13.2	10.2	26.7	41.2
ALT, u/l	30.4	17.4	32.5	18.8	25.4	12.7
AST, u/l	44.0	20.7	45.3	20.6	40.7	21.7
Alkphos, u/l	240.9	84.2	236.2	79.0	257.5	112.5
Glucose, mmol/l	7.1	3.9	7.2	4.2	6.8	3.1
Cerebrospinal fluid results						
Total white cells/microl	208.8	394.3	105.4	150.6	441.4	630.9
Lymphocytes, %	90.4	12.6	92.6	6.3	85.4	20.5
Protein, g/l	1.4	0.9	1.1	0.6	1.9	1.2
Glucose, mmol/l	4.4	2.5	4.5	2.7	4.4	1.8
Glucose, CSF:serum ratio	0.7	0.4	0.7	0.4	0.7	0.3

Hb, haemoglobin; WBC, white blood cells; ESR, erythrocyte sedimentation rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Blood and CSF findings are summarised in Table 2. Thirty-nine (87%) JE+ patients had a CSF result available. CSF generally showed a leucocytosis with a mean white cell count of 209 cells/μl (SD 394, median 50, range 2–1688) with lymphocyte predominance (mean 90%) and elevated protein (mean 1.4, SD 0.9, median 1.1 g/l). In 7 (18%) CSF samples the white cell count was 'normal', i.e. 5 or less, with 6 of these having a raised protein level. The remaining one CSF with normal white cell count (2 cells/μl) and normal protein (0.36 g/l) came from a patient with a compatible history (fever, headache, reduced level of consciousness for 3 days), both sera and CSF were positive for JE and there were persisting cognitive difficulties at discharge. Blood tests generally showed a mild increase in leucocytes and erythrocyte sedimentation rate along with mild elevations of creatinine and liver function tests (Table 2).

Of the 45 JE+ patients, 11 (24%) were dead at hospital discharge, 21 (47%) were alive but with persisting cognitive or other neurological deficit, and 13 (29%) were considered fully recovered. The only significant differences on univariable analysis between those with a poor outcome (P) and the fully recovered (FR), was lower GCS at presentation (mean 9.4 (P) vs. 11.5 (FR), p = 0.05), and lower inflammatory parameters in the CSF (CSF total white cell count mean 105 (P) vs. 441

cells/μl (FR), p = 0.01 and CSF protein 1.1 (P) vs. 1.9 g/l (FR), p = 0.01).

Of the 46 patients with negative tests for JE (hereafter JE-), 27 (59%) had a reasonable alternate diagnosis to JE, which included intracerebral or meningeal tuberculosis, intracerebral haemorrhage, other viral infection, and primary seizure disorder. Twenty-five (54%) of the JE- patients had abnormal CSF results. Altogether 19 (41%) JE- patients had an acute encephalitic presentation, an abnormal CSF, and no alternate diagnosis, 5 of whom (11%) died.

Sixteen (36%) JE+ patients had a CT head scan. Of these, 7 (44%) showed unilateral or bilateral frontal hypodensities, 1 (2%) had a unilateral thalamic hypodensity, 2 (4%) showed evidence of cerebral oedema and 7 (44%) were normal.

Discussion

We have described a cohort of patients with confirmed JE from a single hospital in Sonitpur District Assam, India, during a 6-week outbreak of the disease. The disease had not previously been described in this area; the age distribution of cases suggests a population naïve to the disease with both adults and children affected.[3, 6, 7] Subsequent field testing by the staff at the Indian Council for Medical Research, Regional Medical Research Centre, Dibrugarh, confirmed a low rate of antibodies to the disease in adults from villages where cases were found.

Our results confirm the serious nature of the condition with 24% dying and a further 47% with residual deficits, many serious, at hospital discharge. As reported previously,[8] lower GCS at presentation was associated with worse outcome but less obviously a poorer inflammatory response in the CSF was also associated with worse outcomes. HIV status was not routinely checked in our patients but no HIV cases had been reported in the local population in the previous two years, nor found in routine screening of pregnant women. Our assessment of cognitive function at discharge was very crude and could have missed significant deficits; therefore our associations with 'poor outcome' should be treated with caution.

It is likely that some of our JE- cases actually had JE. The antibody response in blood and CSF can take some days to reach significant levels,[9] and particularly in patients where convalescent samples could not be collected, or who died early after admission, false negative tests are possible. Other diagnostic possibilities include scrub typhus, leptospirosis and infection with West Nile virus, all of which are reported as causes of AES in Assam.[10,11]

Japanese encephalitis compared to herpes simplex encephalitis

Clinicians in Western countries are familiar with the presentation of herpes simplex encephalitis (HSE). A recent large study of acute encephalitis in the UK covering three large geographic areas for 2 years,[12] identified 38 definite cases of HSE. Compared to our JE+ cases, clinical presentation of the HSE cases (rates of fever, headache, personality or behaviour change, focal neurology and GCS), were very similar. For example, in both cohorts the proportion of patients with GCS ≤ 8 at presentation was 24%. CSF findings were also similar. More of the HSE patients had seizures (63% vs. 24%). More of the JE patients died (24% vs. 11%) and length of stay in hospital was much shorter (median 7 days vs. 30 days) for the JE+ patients.

This comparison of the results from JE patients with those with HSE from the UK reveals broad similarities and provides no clear-cut features (apart from recent travel from an endemic area – the incubation period is thought to be 5–15 days[13]) that would help clinicians distinguish these cases from HSE. The higher death rate for the JE cases may reflect differences in the provision and quality of intensive care management. The very much shorter length of stay for JE+ patients (7 vs. 30 days) is probably a reflection of a medical system where patients pay the full cost of their care, incentivising early discharge home rather than indicating milder disease. The risk of JE for travellers in endemic regions is thought to be < 1/1,000,000 visits. Only two cases have ever been reported in the UK.[14]

Prevention of JE requires vaccination of at risk populations. On the basis of our identification of these cases of JE in 2008, a programme was undertaken in a campaign mode between 4 and 22 May 2009 which attempted to vaccinate all children (1–15 years) in the Sonitpur district. Out of a target population of 570,350, 431,387 (76%) were vaccinated (personal communication Additional Chief Medical and Health Officer, Sonitpur). Lyophilised live attenuated SA 14-14-2 JE vaccine, supplied by the Department of Immunization, Ministry of Health and Family Welfare, Government of India, was used for the immunisation programme. The paediatric group vaccination was followed by JE vaccination among the 15–65 year age group from March to May 2015 with 72% coverage reported (personal communication Additional Chief Medical and Health Officer, Sonitpur).

It is likely that JE cases are underreported both in India and worldwide. Our 45 cases from a single small hospital represented 11% of all cases reported to WHO from India in 2008.[15] Many cases throughout India would not have been identified as testing for JE virus has limited availability, usually is a cost to the patient, and a positive result would not lead to a change in treatment as there is no proven effective treatment.

From our experience of this outbreak of JE in an area not previously affected by the disease, we conclude that heightened surveillance with ready access to testing for JE in non-endemic regions, particularly those bordering endemic regions, is appropriate, so that new cases of acute encephalitis syndrome are identified as JE (or other infection) and an appropriate vaccination programme undertaken.[16]

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